Tuberculosis medicines for children in Europe: an unmet medical need

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Shareable abstract (@ERSpublications)
Findings show that the lack of first-line child-friendly anti-TB medicines is considered an unmet medical need in most of the EU/EEA, leading countries to resort to workarounds or importation to overcome gaps in availability https://bit.ly/43dix0k

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Abstract

The availability of first-line medicines for the treatment of drug-susceptible tuberculosis (TB) is inconsistent across European countries. This is particularly worrisome for child-friendly medicines. There are reported examples of physicians being forced to adapt and/or combine formulations intended for adults to treat children with TB. Reduced compliance, unknown effects on treatment outcomes and unpredictable toxicity are potential consequences of resorting to these suboptimal treatment options. Furthermore, the use of these alternatives may increase the risk of drug-resistant TB. This study analysed the availability and use of TB medicines in the European Union (EU)/European Economic Area, with a particular focus on child-friendly formulations. We sought to carry out a full review of the situation by means of a survey involving the EU regulatory network. Countries were asked to confirm marketing status of anti-drug-susceptible-TB medicines, ways used to overcome their absence in their territory and the general difficulties they face to treat children with TB. Results confirmed that rifampicin suspension is the only child-friendly formulation available in Europe, approved in just 10 member states. Overall, 24 countries out of 30 considered the lack of adequate drug-susceptible TB medicines an unmet medical need. To overcome this, countries confirmed that they resort to importation or use adapted formulations. The joint forces of European institutions and pharmaceutical industry are crucial for the development of paediatric formulations and contribute to better compliance and health outcomes.

Introduction

Tuberculosis (TB) is a major global health problem, with an estimated burden of 10 million new cases annually worldwide [1]. It remains one of the leading infectious causes of death globally. In 2020, an estimated 1.5 million people died from the disease. Children, especially aged <5 years, are particularly at risk of progressing from infection to the disease stage and of developing severe forms of the disease as well as extrapulmonary TB, with high case fatality [2]. Although most cases are reported in low-resource settings (particularly in sub-Saharan Africa and Asia), TB also occurs in the European region, where it makes up for a small fraction of the disease globally.

The latest available incidence data from the World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) [3] show ~33 000 TB cases in total in the European Union (EU)/European Economic Area (EEA) (figure 1), with a geographical distribution skewed towards the eastern border of the Union, where a few countries (Romania, Lithuania, Bulgaria) are accountable for a large proportion of the total number of TB cases. Romania reported almost a quarter of all cases in 2020. Cases reported in children aged <15 years were ~1200, making up 3.7% of cases in the EU/EEA countries. The proportion of TB cases notified in children aged <15 years varied from <1% (*e.g.* Slovenia, Czechia and Estonia) to 22.2% (Slovakia) of all cases (table 1) [5].

For the treatment of new adult patients with pulmonary drug-susceptible TB, the therapeutic guidelines (*e.g.* by the WHO [6] and the European Respiratory Society and American Thoracic Society [7]) recommend

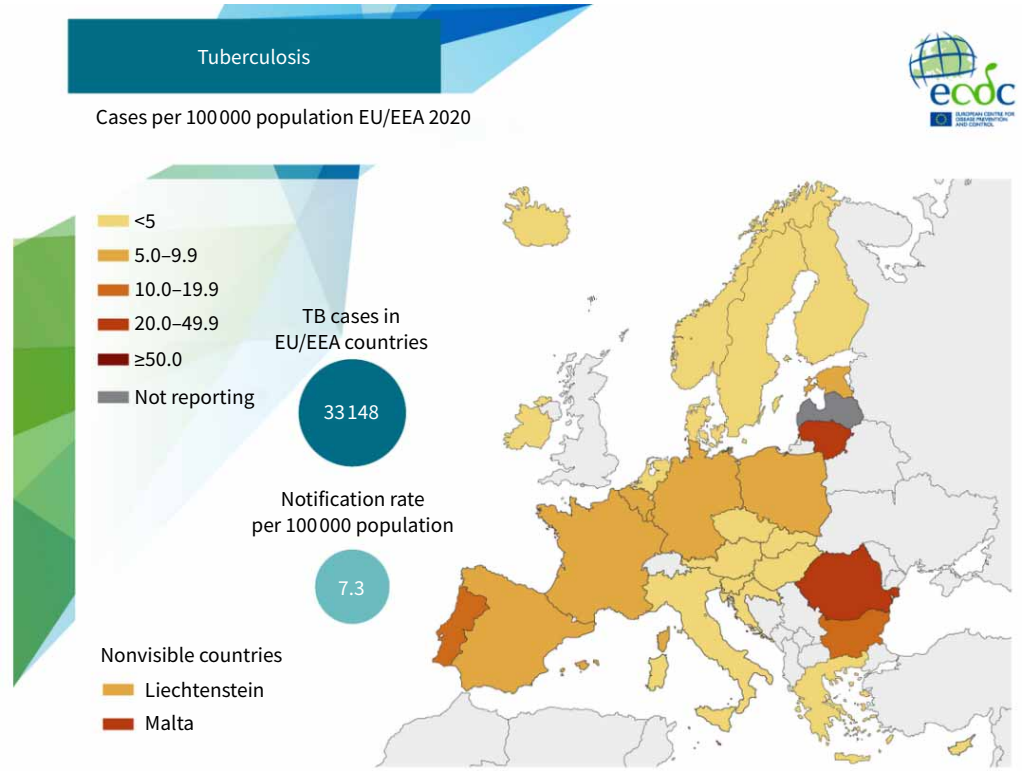

FIGURE 1 Tuberculosis (TB) cases in the European Union (EU)/European Economic Area (EEA) per 100 000 population by country, 2020. Reproduced from [4] with permission.

a 6-month scheme that includes four antibiotics, namely 2 months with four medicines: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (HRZE), followed by 4 months with only the first two: H+R (HR).

Currently in the EU, first-line TB products are authorised only in some member states *via* the so-called national, mutual recognition or decentralised procedures, which allow country selection by pharmaceutical companies. This differs from the centralised authorisation procedure, where pharmaceutical companies submit a single marketing authorisation application to the European Medicines Agency (EMA), making medicines available throughout the EU on the basis of a single marketing authorisation.

First-line products adequate to reduce the pill-burden or ease ingestion, available elsewhere in the globe (*e.g.* fixed-dose combinations (FDCs), liquid formulations, or both), are scarce in Europe.

This situation is particularly worrisome when it comes to child-friendly formulations, where a potential unmet medical need (*i.e.* a condition for which there is no satisfactory method of diagnosis, prevention or treatment [8]) exists.

The Inventory of Paediatric Therapeutic Needs published by the EMA since 2021 describes different therapeutic areas where research and development of medicinal products for children are needed in the EU [9]. In this inventory, isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) are identified as needed medicines for the treatment of TB. It also specifies that data on pharmacokinetics and dosing are lacking, alongside child-friendly FDCs of HRZE, HRZ and HR.

Treating drug-susceptible TB in children is known to be particularly difficult [10] due to the complexity of multiple medicines to be taken daily over an extended period of time (the length of treatment recommendations for children [11], albeit having been recently shortened to 4 months by reducing the second two-drug (H+R) treatment period from 4 to 2 months [12], is still an extended treatment), and the fact that development of child-friendly formulations of anti-TB medicines has been neglected [10].

TABLE 1 Numbers of tuberculosis (TB) cases notified in all age groups and in children in 2020 in the European Union

	All TB notifications (adults+children)	TB notifications (children aged 0–14 years)	Cases reported in children, %
Austria	388 (1.2)	12 (1.0)	3.1
Belgium	830 (2.5)	48 (3.9)	5.8
Bulgaria	930 (2.8)	24 (2.0)	2.6
Croatia	183 (0.5)	2 (0.2)	1.1
Cyprus	36 (0.1)	0 (0)	0
Czechia	367 (1.1)	2 (0.2)	0.5
Denmark	221 (0.7)	10 (0.8)	4.5
Estonia	124 (0.4)	1 (0.1)	0.8
Finland	174 (0.5)	5 (0.4)	2.9
France	4606 (13.9)	191 (15.7)	4.1
Germany	4127 (12.5)	163 (13.4)	3.9
Greece	396 (1.2)	17 (1.4)	4.3
Hungary	406 (1.2)	5 (0.4)	1.2
Iceland	12 (0)	2 (0.2)	16.7
Ireland	240 (0.7)	5 (0.4)	2.1
Italy	2287 (6.9)	100 (8.2)	4.4
Latvia	Not reported	Not reported	Not reported
Lithuania	726 (2.2)	13 (1.1)	1.8
Luxembourg	34 (0.1)	0 (0)	0
Malta	140 (0.4)	7 (0.6)	5
The Netherlands	623 (1.9)	19 (1.6)	3.0
Norway	160 (0.5)	11 (0.9)	6.9
Poland	3388 (10.2)	38 (3.1)	1.1
Portugal	1445 (4.4)	42 (4.5)	2.9
Romania	7698 (23.2)	261 (21.4)	3.4
Slovakia	158 (0.5)	35 (2.9)	22.2
Slovenia	77 (0.2)	0 (0)	0
Spain	3044 (9.2)	188 (15.4)	6.2
Sweden	328 (1.0)	16 (1.3)	4.9
Total, n	33 148	1217	3.7

Data are presented as n (%), unless otherwise stated. Data from [5].

European paediatricians have been highlighting the need for paediatric formulations for the treatment of susceptible TB (preferably in FDCs), as, out of the four medicines in the regimen, the only first-line child-friendly formulations approved and available in the EU are for rifampicin alone. This is in line with data published in 2021 describing the availability gaps in the therapeutic armamentarium for TB in Europe [13].

However, the countries where child-friendly products are available differ between publications, previous surveys, WHO data and the extended EMA's EudraVigilance Medicinal Product Dictionary (xEVMPD, also known as "Article 57 database") [14]. In the absence of child-friendly options, treating physicians must resort to alternatives, such as imported paediatric FDCs [13]. In addition, publications and sporadic reports suggested that suspensions or weight-adapted powder mixes are prepared *ad hoc* by pharmacies from capsules, and that breaking tablets (halved or cut, crushed or chewed directly) or mixing them with food or water are common off-label workarounds [13, 15]. In the context of the recommended multidrug regimen, these practices translate into unreliable dosing [16] and further palatability problems [10, 17]. Apart from the unknown effects on toxicity, the main concern is poor compliance [17, 18]. In turn, this may lead to insufficient dosages [10], potentially resulting in treatment failure, induction of microbial resistance, or both, after first-line treatment [2, 10]. In either case, patients may be declared as having drug-resistant TB, thus requiring second-line treatment, and potentially inducing even further antimicrobial resistance (to the second-line medicines).

Although the overall rates of childhood TB are decreasing in the EU/EEA, childhood TB has been rising in certain countries [19]. Recent manufacturing problems have also highlighted vulnerability of TB medicines supply in the EU, and there have been concerns that a potential increase in demand due to the

influx of refugees into the EU from areas with high TB prevalence (*e.g.* currently from Ukraine), is likely to worsen the problem.

Despite rather high numbers of reported cases of TB in children in the EU (1217 in 2020; table 1), the WHO was only aware of very few examples of procurement attempts by TB treating centres and hospitals to circumvent the gaps described herein (unpublished data).

To disentangle the aforementioned discrepancies in data on how many child-suitable formulations are available and where, particularly in terms of first-line medicines for drug-susceptible TB, an analysis aiming to assess their availability in the EU/EEA was carried out by conducting a survey in the countries concerned, whereby members of the European Medicines Regulatory Network were contacted and asked to describe which first-line anti-TB medicines (*e.g.* adult and/or child-friendly formulations of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z)) were available in their territory. As part of this exercise, the opportunity was taken to also ask member states to illustrate the methods used to overcome the lack of availability. Finally, we aimed to ascertain whether there were patterns within the Union (*e.g.* geographical).

Methods

To clarify which TB medicines were authorised in each country and to confirm the data entered by companies into the "Article 57 database", the EMA mobilised the EU regulatory network. A two-step survey was conducted, making use of EU regulatory fora coordinated by the EMA. The survey was run first canvassing member states *via* the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh; www.hma.eu/human-medicines/cmdh/about-cmdh.html). Member states were asked to provide updated availability and marketing authorisation data of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) in their territory.

Additionally, the following questions specific to paediatric TB were included in the survey (supplementary material): 1) practices used to tackle the lack of available child-adequate formulations; 2) whether member states considered the situation to constitute an unmet medical need; and 3) suggestions on how to address the issue (optional).

After this, as a second step to maximise the response rate and increase granularity of the answers, the same survey was distributed using the single point of contact (SPOC), a network whose role is to improve information sharing between member states, the EMA and the European Commission on important medicine shortages and to coordinate actions to help prevent and manage them. This second round complemented the answers from CMDh, and added clarity, particularly on the optional answers.

The pool of participants included all the EU/EEA countries. Participants were not limited to one answer per question, and could therefore list as many solutions/suggestions as they wished, where applicable.

The period from presentation of the project to CMDh to the end of data collection and analysis was January–June 2022. Following collection, data were analysed by the authors in June 2022.

Results

Response rate was 100% (30 countries).

A clear breakdown of what is approved and marketed in the various countries emerged, as the survey enabled mapping a complete and up-to-date picture of the availability of first-line anti-TB medicines in Europe. Table 2 details it: Estonia does not have any such medicines approved; Liechtenstein only has one; Cyprus, Croatia and Iceland have two; Greece, Latvia, Luxembourg, Slovakia and Slovenia have three. The majority of European countries have five TB medicines approved (Denmark, Germany, Hungary, Ireland, Poland and Romania). Some European countries have seven (Portugal) or eight first-line anti-TB medicines approved (France and Spain).

For adult formulations, only 13 countries (Austria, Belgium, Bulgaria, Finland, France, Germany, Hungary, Malta, the Netherlands, Poland, Portugal, Romania and Spain) have availability of all four first-line anti-TB medicines.

For adult FDCs, while HR is available in 18 (60%) out of 30 countries, HRZ is only available in France, Italy, Ireland, Norway, Portugal, Slovenia, Spain and Sweden (26.7%). HRE is not available anywhere and

TABLE 2 First-line anti-tuberculosis medicines available in Europe (as of March 2022). For this analysis, the term "child-friendly formulations" includes "dispersible tablets" and "liquid formulations"

	Adult formulations				Adult FDCs				Child-friendly formulations			
	R	H	Z	E	H+R	H+R+Z	H+R+E	H+R+Z+E	R	H	Z	E
Austria	✓	✓	✓	✓	✓	×	×	×	✓	×	×	×
Belgium	✓	✓	✓	✓	×	×	×	×	×	×	×	×
Bulgaria	✓	✓	✓	✓	×	×	×	×	×	×	×	×
Croatia	✓	×	✓	×	×	×	×	×	×	×	×	×
Cyprus	✓	×	×	×	✓	×	×	×	×	×	×	×
Czechia	✓	✓	×	✓	×	×	×	×	×	×	×	×
Denmark	✓	✓	✓	×	✓	×	×	✓	×	×	×	×
Estonia	×	×	×	×	×	×	×	×	×	×	×	×
Finland	✓	✓	✓	✓	×	×	×	×	×	×	×	×
France	✓	✓	✓	✓	✓	✓	×	✓	✓	×	×	×
Germany	✓	✓	✓	✓	×	×	×	×	✓	×	×	×
Greece	×	✓	✓	×	✓	×	×	×	×	×	×	×
Hungary	✓	✓	✓	✓	✓	×	×	×	×	×	×	×
Iceland	✓	✓	×	×	×	×	×	×	×	×	×	×
Ireland	✓	×	×	✓	✓	✓	×	×	✓	×	×	×
Italy	✓	✓	×	✓	✓	✓	×	×	✓	×	×	×
Latvia	✓	×	✓	✓	×	×	×	×	×	×	×	×
Liechtenstein	×	×	×	✓	×	×	×	×	×	×	×	×
Lithuania	✓	×	✓	✓	✓	×	×	×	×	×	×	×
Luxembourg	✓	✓	✓	×	×	×	×	×	×	×	×	×
Malta	✓	✓	✓	✓	✓	×	×	×	✓	×	×	×
The Netherlands	✓	✓	✓	✓	✓	×	×	×	✓	×	×	×
Norway	✓	×	×	×	✓	✓	×	✓	×	×	×	×
Poland	✓	✓	✓	✓	✓	×	×	×	×	×	×	×
Portugal	✓	✓	✓	✓	✓	✓	×	×	✓	×	×	×
Romania	✓	✓	✓	✓	✓	×	×	×	×	×	×	×
Slovakia	✓	✓	×	✓	×	×	×	×	×	×	×	×
Slovenia	×	×	✓	×	✓	✓	×	×	×	×	×	×
Spain	✓	✓	✓	✓	✓	✓	×	✓	✓	×	×	×
Sweden	✓	✓	×	×	✓	✓	×	✓	✓	×	×	×

FDC: fixed-dose combination; R: rifampicin; H: isoniazid; Z: pyrazinamide; E: ethambutol.

HRZE is only available in Denmark, France, Norway, Spain and Sweden (16.7%). None of the countries has all four options.

Hence, table 2 illustrates the patchiness across Europe in terms of availability of FDCs, with a geographical distribution of approved FDCs showing little or no correlation with the incidence of TB in the country of approval (compare with figure 1). Of note, no member state reported availability of paediatric FDCs.

With regards to child-friendly formulations, rifampicin suspension is the only liquid formulation available in the EU/EEA and it is only available in 10 (Austria, France, Germany, Ireland, Italy, Malta, the Netherlands, Portugal, Spain and Sweden) (33.3%) out of 30 countries. Consequently, two-thirds of EU/EEA countries do not have any child-suitable formulation approved, as emphasised by the simple visualisation in table 2, and that no other child-friendly formulation exists in Europe, neither liquid nor dispersible tablets.

24 (80%) out of the 30 canvassed countries considered that the lack of first-line child-friendly drug-susceptible TB medicines constitutes an unmet medical need. When these are mapped by population, they represent >93% of the population covered by the survey (figure 2).

Analysis of the survey also allowed clarification of what has been done to circumvent the availability gaps. 18 member states stated that they "import from other markets". 22 answered that adapted formulations are

FIGURE 2 European countries that consider that there is an unmet medical need for child-friendly anti-tuberculosis medicines (as of March 2022).

used, such as “magistral”, “weight-adapted” or “crushed adult” formulations. Some national guidelines (*e.g.* Spain [20], Ireland [21] and Germany [22]) even envisage *ad hoc* paediatric preparations from adult formulations approved in those countries.

When asked to describe what would help to overturn the situation, 20 (83.3%) out of 24 countries who consider the unavailability of first-line child-friendly medicines for drug-susceptible TB to be an unmet medical need provided at least one interpretable suggestion/proposal. Four answers were too unspecific to be analysed. It has to be borne in mind that more than one suggestion could be given.

All 20 countries answered that they would like to have liquid formulations (figure 3). 11 elaborated that it could be of the individual components. Eight said it could be “child-friendly FDCs” and five would like either of the above (figure 4).

Five responders identified “dispersible tablets” as a possible solution. Of note, “dispersible tablets” and “liquid formulations” were grouped together when interpreting the answers, as they would ultimately result in a liquid form when taken by patients.

Two responders indicated “tablets with lower strength” as desirable.

Discussion

The results of the survey on first-line anti-TB medicines confirmed that the data available in the Article 57 database and figures from previous attempts to measure availability [13] of the four first-line anti-TB medicines were incomplete due to differences regarding either approved medicines not included in the Article 57 database or medicines that were included despite being no longer approved. Cases of products approved, but not actually marketed (*i.e.* thus not available to hospitals or pharmacies), were also brought to light. Additionally, the notion that there are availability gaps across EU/EEA for these medicines was corroborated by the results: there is ample heterogeneity among the canvassed countries (*i.e.* Estonia has no first-line anti-TB medicines; France and Spain have as many as eight).

Big access problems are evident for FDCs, where the geographical distribution of approved FDCs has little or no correlation with the incidence of TB in the country of approval (for instance Romania, the country

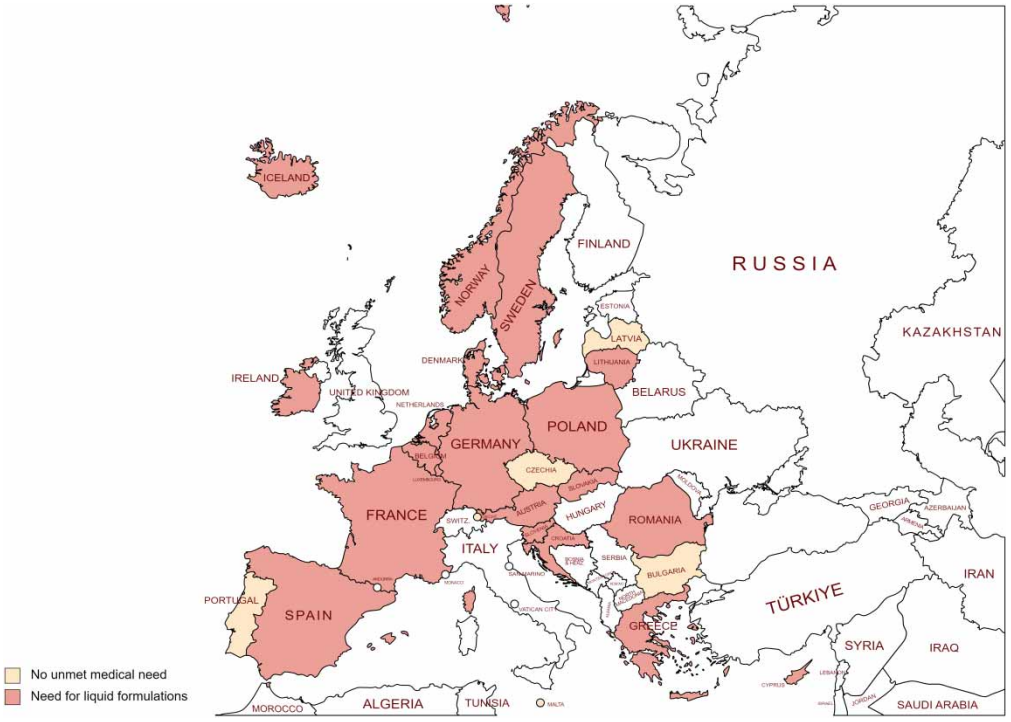

FIGURE 3 European countries in need of liquid formulations of first-line anti-tuberculosis medicines.

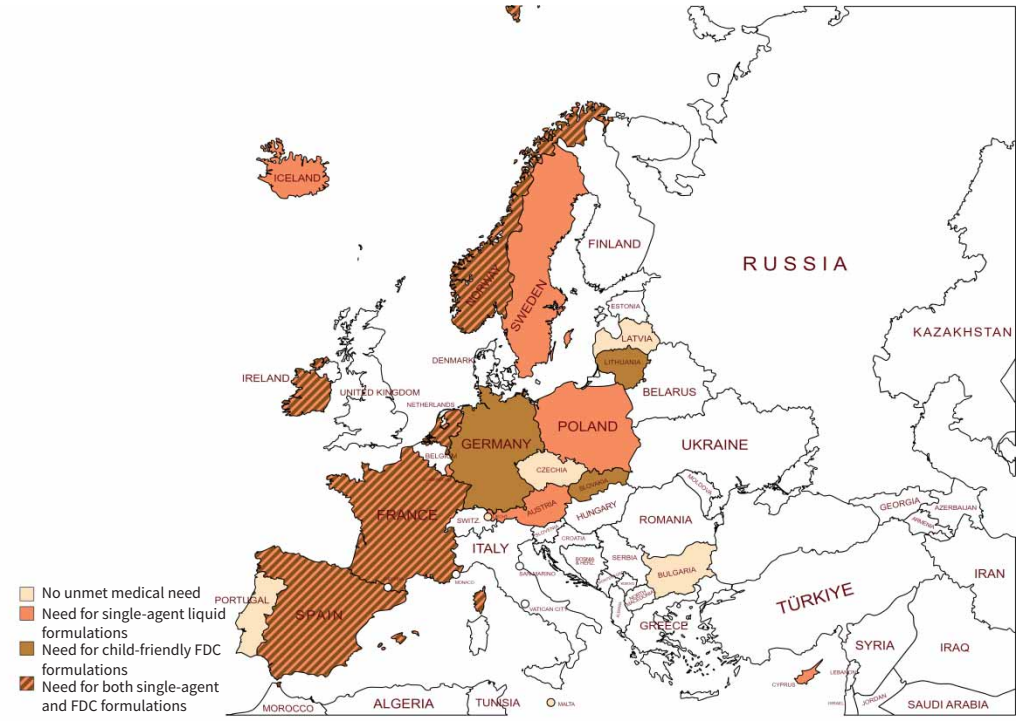

FIGURE 4 Detailed anti-tuberculosis formulations needed by European countries. Belgium, Croatia, Denmark, Greece, Romania and Slovenia did not specify for which medicinal products a liquid formulation is required. FDC: fixed-dose combination.

with the highest number of reported cases has only one FDC approved; figure 1 and table 2). The challenges are even bigger for paediatric formulations, as the only child-friendly formulation approved in EU/EEA, rifampicin suspension, is only available in 10 (33.3%) member states. Slovakia, the country with the highest proportion of TB cases in children (22.2%), has no child-friendly formulations at all. It can be observed that the availability of first-line medicines against TB in the EU/EEA is inconsistent for adults and totally inadequate for children.

The majority of member states considered the lack of first-line child-friendly anti-TB medicines an unmet medical need. While their answers do not always show a direct link with the incidence of paediatric TB, the analysis of the data enabled mapping of the situation and creating the foundation of an evidence-based "need case" for first-line child-friendly anti-TB medicines of single-agent and FDC formulations in Europe.

Six countries did not consider the situation to constitute an unmet medical need. This was the case for Malta and Bulgaria, who did not explain the reasons, despite the prevalence of TB in those countries. Portugal clarified that child-friendly preparations are carried out at national level under the control of military pharmaceutical laboratories, following controlled methods. Similarly, explanations from Czechia suggest that they are satisfied with magistral formulations prepared in cooperation with hospital pharmacies or *ad hoc* preparation of suspensions/crush adult formulations. For Latvia and Liechtenstein, the lack of child-friendly anti-TB medicines does not constitute an issue due to the negligible paediatric population with TB in their territories.

The results of the survey show that besides child-friendly FDCs such as those available elsewhere in the world, EU/EEA countries see the need for age-appropriate paediatric formulations of the single-active agents (figure 4). This may be attributable to an expected higher therapeutic flexibility achievable with the latter from a clinical point of view in terms of combining actives and personalised dose adjustments. The flexibility achieved with these formulations would enable the prevention of suboptimal treatment for susceptible TB, thus reducing the chances of treatment failure and possible induction of microbial resistance within first-line treatment. However, some countries specified that mono-component child-friendly products would be only seen as a first step in a longer plan to then have them combined as FDCs. In this context, it is worth noting that this is compatible with the known WHO preference for dosage forms such as tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups (*e.g.* dispersible and soluble tablets), and appropriate for global use for practical reasons such as their less bulky nature in view of transport, easier storage, *etc.* [23].

The data shown in this article have informed exchanges with EU/EEA regulatory agencies and other institutions and will be used to raise awareness when interacting with the pharmaceutical industry in the context of the EMA contribution to the WHO project of reversing the TB epidemic in Europe [24]. That unmet medical need has been established will help the EMA to target its efforts when assisting potential applicants intending to market child-friendly first-line medicines for drug-susceptible TB in the EU through the existing regulatory pathways. This will be relevant to the EMA's efforts to promote adequate medicines for children [25]. Since there is a potential correlation between lack of compliance with TB treatments in children and emergence of antimicrobial resistance, this could also contribute to the EMA's work to combat antimicrobial resistance [26].

Conclusions

The survey provides an up-to-date picture of the current situation regarding the availability of first-line anti-TB medicines in the EU/EEA. The majority of member states included in this analysis have identified that there is an unmet medical need, in particular when it comes to child-friendly formulations, and physicians are forced to adapt what is available on the market in order to treat children. Due to external shock factors, such as recent manufacturing problems having an impact on TB medicine supply and a predicted increase in demand associated with the influx of Ukrainian refugees to the EU, future improvements of the situation are not expected.

TB is a curable disease and all actors of the health value chain, including the pharmaceutical industry and public health bodies, need to play their role to shape the market and end TB by 2035, as established by the WHO [24]. The EMA stands ready to play its part in addressing this public health issue by supporting applicants for first-line child-friendly anti-TB medicines. The pharmaceutical industry is encouraged to engage with the agency to optimise their development plans so that these medicines can reach patients.

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